Update on Anti-Resorptive Therapy: Focus on Transitioning from Denosumab

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Steven T Harris MD FACP FASBMR
Clinical Professor of Medicine
University of California, San Francisco
steve.harris@ucsf.edu

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Disclosure and Conflicts of Interest Steven T Harris MD 2021-2022

- **Speakers Bureaus and Consulting**
  - **Amgen**
  - **Radius Health**

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Key Topics

- **Brief review of bone remodeling**
- **Mechanism of action of pharmacologic osteoporosis therapies**
- **Why "transition" from one therapy to another?**
- **Transitioning from denosumab therapy**

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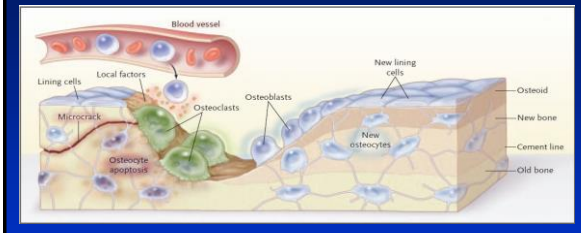
Bone Structure and Physiology



Osteoclasts remove old bone. Osteoblasts make new bone. Osteocytes detect mechanical stress and microcracks and direct the activity of osteoclasts and osteoblasts.

Seeman E, et al. *N Engl J Med* 2006;354:2250

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Normal Coupling of Bone Remodeling

Resorption = Formation

- Most treatment agents (bisphosphonates, SERMs, calcitonin, estrogen, denosumab) act primarily on the left side of the equation—to decrease bone resorption
- A decrease in resorption is followed by a decrease in formation—and BMD improvement tends to "plateau" after several years (with the exception of denosumab…)
- Of contemporary treatment agents, only teriparatide, abaloparatide and romosozumab act on the right side of the equation—to stimulate formation

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Treatment Summary

- We have the tools to identify patients at risk; in FRAX©, bone mineral density (BMD), age and previous fractures in particular are strong, independent predictors of fracture risk
- Treatments significantly decrease fracture risk:
  - "Antiresorptive" ("anti-remodeling") therapy produces a modest BMD increase, yet decreases fracture risk—especially in the spine—much faster and to a larger extent than predicted by the relatively small change in BMD; this implies an important improvement in bone "quality"
  - Anabolic therapy with teriparatide (or abaloparatide or romozosumab) increases BMD more than antiresorptive treatment, with reasonable evidence that fracture protection is greater

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Anabolic Agents
Teriparatide, Abaloparatide, Romozosumab

Approved for Patients at "High Risk for Fracture"

- History of osteoporotic fracture, or
- Multiple risk factors for fracture, or
- Patients who have failed or are intolerant to other available osteoporosis therapy

Forteo, Tymlos and Evenity Prescribing Information

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When Might a Treatment Transition Occur?

- "Patients who have failed or are intolerant to other available osteoporosis therapy"
  - Patients who have fractured on current treatment
  - Patients who remain at high risk of fracture despite current treatment—so-called "treat to target" approach
  - Patients who have an obstacle to continuing current treatment
    - Side effects, cost, route of administration, logistics

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A Common Management Problem: Transitioning from Denosumab

- Is it necessary to stop denosumab therapy after a certain number of years?
  - No. At least based on the 10-year FREEDOM extension trial
  - Stopping denosumab is associated with relatively rapid bone loss and a risk of multiple vertebral fractures ("MVF")

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Denosumab

- Monoclonal antibody to RANKL
- 60 mg subcutaneous injection every 6 months
- 9% increase in spinal BMD after 3 years in the pivotal FREEDOM trial; 4%-5% increase in hip BMD
- Reduction in fracture risk after 3 years:
  - 68% decrease in new vertebral fractures
  - 40% decrease in hip fractures
  - 20% decrease in nonvertebral fractures
- 10-year data: continued increase BMD, reduced bone turnover, good safety

Cummings SR et al. *N Engl J Med*. 2009;368:756-765
Prolia (prescribing information). Thousand Oaks, CA: Amgen; June 2012.
McClung MR et al. *Osteoporos Int*. 2012 July 10 (epub ahead of print).

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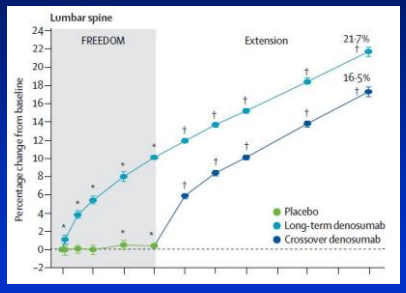
Denosumab: Long-Term Extension



Bone HG et al. *Lancet Diabetes Endocrinol* 2017;513-23

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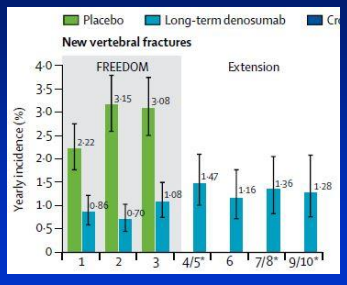
Denosumab: Long-Term Extension



Bone HG et al. *Lancet Diabetes Endocrinol* 2017;513-23

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Denosumab Adverse Events

Adverse events that occurred more commonly in denosumab group (as listed in the PI):

- Hypocalcemia
- Serious infections leading to hospitalization
- Dermatitis, eczema, rashes
- Back pain, pain in the extremity, musculoskeletal pain, hypercholesterolemia, cystitis
- Pancreatitis
- Osteonecrosis of the jaw
- Atypical subtrochanteric and diaphyseal femoral fractures
- Significant suppression of bone remodeling

Prolia® (Prescribing Information). Thousand Oaks, CA: Amgen; revised 09/12.

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"Clinical Features of 24 Patients With Rebound-Associated Vertebral Fractures After Denosumab Discontinuation: Systematic Review and Additional Cases"

- 24 postmenopausal women with a total of 112 vertebral fractures after treatment discontinuation
- Mean number of fractures: 4.7 per patient
- All fractures occurred 8 to 16 months after the last denosumab injection
- No non-vertebral fractures noted during follow up
- 83% of the patients were treatment-naïve
- 33% had prevalent vertebral fractures

Anastasilakis AD et al. *J Bone Miner Res* 2017;32:1291-1296

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Prolia Prescribing Information
As of the January 2017 Update

Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia Treatment

Following discontinuation of Prolia treatment, fracture risk increases, including the risk of multiple vertebral fractures. Cessation of Prolia treatment results in markers of bone resorption increasing above pretreatment values then returning to pretreatment values 24 months after the last dose of Prolia. In addition, bone mineral density returns to pretreatment values within 18 months after the last injection.

New vertebral fractures occurred as early as 7 months (on average 19 months) after the last dose of Prolia. Prior vertebral fracture was a predictor of multiple vertebral fractures after Prolia discontinuation. Evaluate an individual's benefit/risk before initiating treatment with Prolia.

If Prolia treatment is discontinued, consider transitioning to an alternative antiresorptive therapy.

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Change after Stopping Denosumab

In a Phase II, dose-ranging study of denosumab, patients were randomized to nine different arms, including:

Months 0 to 24	Months 24 to 36	Months 36 to 48
Placebo	Placebo	Placebo
Dmab 210 mg q 6m	Placebo	Placebo
Dmab 30 mg q 3 m	Placebo	Dmab 60 mg q 6 m
Alendronate	Discontinued	Discontinued

Miller PD et al. *Bone* 2008;43:222-9

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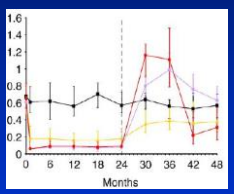
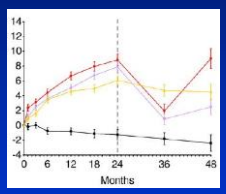
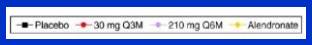
Change after Stopping Denosumab

Serum CTx (C-telopeptide)



Spine BMD





Miller PD et al. *Bone* 2008;43:222-9

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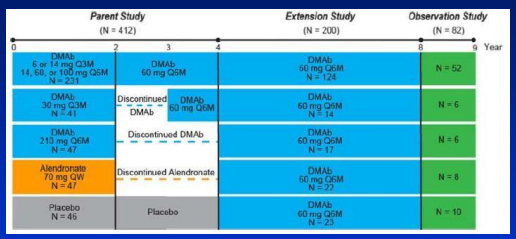
Change after Stopping Denosumab
9-Year Phase II Extension Study Design



52 patients for followed for one year after completing 8 years of denosumab therapy; 17 of 52 patients received osteoporosis treatment during that year

McClung MR et al. *Osteoporosis Int* 2017;28:1723-1732

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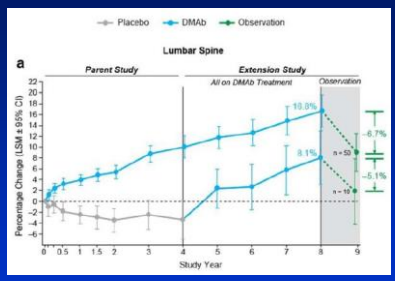
Change after Stopping Denosumab
9-Year Phase II Extension Study: Spinal BMD



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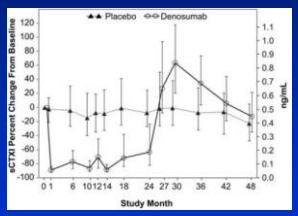
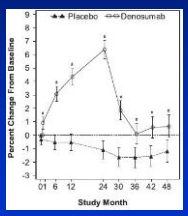
Change after Stopping Denosumab
Denosumab 60 mg Every 6 Months for 24 Months

Serum CTx (C-telopeptide)



Spine BMD



Bone HG et al. *J Clin Endocrinol Metab* 2011;96(4):972-980

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Vertebral Fractures After Denosumab Discontinuation FREEDOM/Extension Post-Hoc Analysis

- Participants received ≥ 2 doses of denosumab or placebo and remained in the study for ≥ 7 months
- 1471 participants (1001 denosumab, 470 placebo)
- On denosumab treatment: 1.2 vertebral fractures/100 pt-yrs
- On placebo treatment: 7.0 vertebral fractures/100 pt-yrs
- After denosumab treatment: 7.1 vertebral fractures/100 pt-yrs
- After placebo treatment: 8.5 vertebral fractures/100 pt-yrs

Cummings SR et al. *J Bone Miner Res* 2018;33:190-198

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Vertebral Fractures After Denosumab Discontinuation FREEDOM/Extension Post-Hoc Analysis

- 56 patients formerly on denosumab had at least one vertebral fracture
- 34 (60.7% with multiple vertebral fractures)
  - 21 with 2-3 new fractures
  - 13 had ≥ 4 new fractures
- Rate of multiple vertebral fractures
  - After discontinuing denosumab: 4.2 per 100 pt-yrs
  - After discontinuing placebo: 3.2 per 100 pt-yrs
- Rates of non-vertebral fractures:
  - After discontinuing denosumab: 2.8 per 100 pt-yrs
  - After discontinuing placebo: 3.8 per 100 pt-yrs

Cummings SR et al. J Bone Miner Res 2018;33:190-198

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Change after Stopping Denosumab

- Stopping denosumab is associated with a brisk increase in bone resorption and a corresponding decrease in BMD
- That increase in bone remodeling after stopping has been associated with an increased risk of multiple vertebral fractures ("MVF")

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Change after Stopping Denosumab

- What happens if therapy is switched from denosumab to teriparatide?

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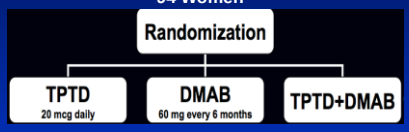
DATA Study

Denosumab And Teriparatide Administration Study

94 Women



- Single-center study
- 2-year Randomized Controlled Trial
- 2-year extension study

Leder BZ, Tsai JN, et al. *J Clin Endocrinol Metab* 2014;99(5):1694-1700
Leder BZ, Tsai JN, et al. *Lancet* 2015;386 (9999):1147-55 (Epub 02 JUL 15)

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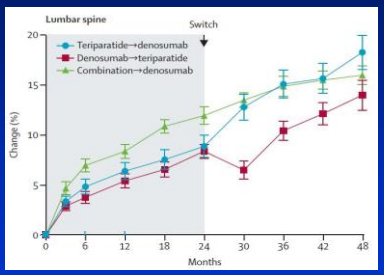
DATA-Switch Study

Denosumab And Teriparatide Administration Study



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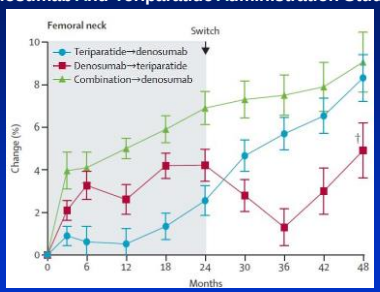

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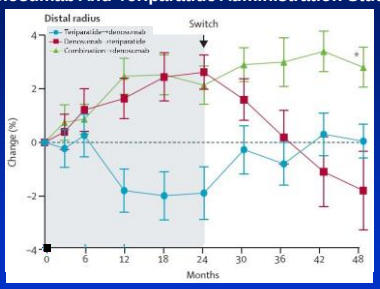

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Leder BZ, Tsai JN, et al. *Lancet* 2015;386 (9999):1147-55 (Epub 02 JUL 15)

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Change after Stopping Denosumab

- What happens if therapy is switched from denosumab to teriparatide?
  - Switching leads to a decrease (at least transient) in BMD that is more pronounced at sites rich in cortical bone
    - The effect on fracture risk is unknown—but it is not likely to be beneficial
  - By extrapolation, switching from denosumab to abaloparatide is not likely to be favorable either

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Change after Stopping Denosumab

- What happens if therapy is switched from denosumab to an antiresorptive?
  - Switching from denosumab to an oral bisphosphonate (alendronate or risedronate) or a SERM (raloxifene) has not proven effective in preventing bone loss entirely
  - Switching to a more potent antiresorptive agent—iv zoledronic acid—is another possible option

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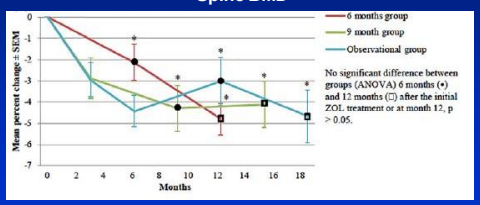
Zoledronic Acid after Denosumab

Zoledronic acid administered at the time of the next scheduled denosumab injection—or 3 months later

Spine BMD



Solling AG et al. *J Bone Miner Res* 2020;35(10):1858-1870

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Change after Stopping Denosumab

- Stopping denosumab is associated with a brisk increase in bone resorption and a corresponding decrease in BMD
- That increase in bone remodeling after stopping has been associated with an increased risk of multiple vertebral fractures ("MVF")
- Switching to another antiresorptive agent does not fully protect against that increased bone resorption
  - That is true even if zoledronic acid is administered when the next denosumab injection is due—or after a delay of 3 months

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Common Management Problems

- Is it necessary to stop denosumab therapy after a certain number of years?
- Probably not. Extended therapy is associated with persistently-low fracture rates, even after a decade
- Treatment is associated with AFF and ONJ, but the absolute risks again appear to be relatively small
- If treatment is to be discontinued, it appears to be best to transition to another antiresorptive therapy—but the optimal way to do so is a matter of active ongoing clinical investigation

ST Harris, personal opinion

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